REMARKS

Claims 1-8 are canceled. Claims 9-21 are pending.

Support for Amendments

Claims 9-14, and 18-19 are amended with respect to a preferred embodiment where the cruciferous indole compound is as specified. Support can be found on page 6, last paragraph, page 7, last paragraph, and page 8, lines 1-3. Claims 14-17 are amended to remove improper multiple dependencies according to US practice. New claims 20 and 21 are presented as preferred embodiments. Support can be found on page 6, last paragraph, and page 8, lines 1-3. In addition, the claims are amended for grammar and form according to US practice.

No new matter is added.

Information Disclosure Statement

A supplemental Information Disclosure Statement was filed on March 21, 2008. Applicants respectfully request consideration of the IDS.

Objection to the Specification

The Office Action objects to the use of "Et-743" without first spelling out the abbreviation. The Office Action also objects to improper multiple dependencies in claims 14-17. By amendment, the term "Ecteinascidin 743" is added to claim 9, and the improper multiple dependencies are removed. Applicants respectfully request withdrawal of the objection and examination of the claims on the merits.

Rejections Under 35 U.S.C. § 101/ § 112, second paragraph

Claims 1-8 are rejected as "use of" claims without active, postive steps. By amendment, claims 1-8 are canceled. Applicants respectfully request withdrawal of the rejection.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-4, 6-13, and 18 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Office Action argues that the phrase "cruciferous indole compound" lacks sufficiently detailed, relevant identifying characteristics. Applicants respectfully traverse. However, in order to advance prosecution, the term "cruciferous indole compound" is replaced with the phrase "indole-3-carbinol or one or more derivatives or pharmaceutically acceptable salts thereof," wherein the indole-3-carbinol derivatives are selected from: 5-methyl-indole-3-carbinol, 5-ethyl-indole-3-carbinol, 5-propyl-indole-3-carbinol, 5-butyl-indole-3-carbinol, 5-pentyl-indole-3-carbinol, 5-methoxy-indole-3-carbinol, 5-ethoxy-indole-3-carbinol, 5-propyloxy-indole-3-carbinol, 5-butyloxy-indole-3-carbinol, 5-amyloxy-indole-3-carbinol, N-methyl-indole-3-carbinol, N-ethyl-indole-3-carbinol, N-propyl-indole-3-carbinol, N-butyl-indole-3-carbinol, N-pentyl-indole-3-carbinol, 2-methyl-indole-3-carbinol, 2-ethyl-indole-3-carbinol, 2-propyl-indole-3-carbinol, 2-butyl-indole-3-carbinol and 2-pentyl-indole-3-carbinol.

In view of the support for the amendment on pages 6-8 of the specification, Applicants respectfully request withdrawal of the rejection.

Claims 1-9 and 11-13 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement for the entire scope of the claims. The Office Action argues that while the specification is enabling for the use of indole-3-carbinol to counteract hepatotoxicity, it fails to

enable cruciferous compounds in general to counteract side effects, and fails to enable indole-3-carbinol to counteract side effects other than hepatotoxicity (pages 5-10 of the Office Action). Applicants respectfully traverse. However, in order to advance prosecution, hepatotoxicity is specified as the side effect to be reduced in claim 9. In addition, the term "cruciferous indole compound" is replaced with the phrase "indole-3-carbinol or one or more derivatives or pharmaceutically acceptable salts thereof," wherein the indole-3-carbinol derivatives are selected from: 5-methyl-indole-3-carbinol, 5-ethyl-indole-3-carbinol, 5-propyl-indole-3-carbinol, 5-butyl-indole-3-carbinol, 5-pentyl-indole-3-carbinol, 5-methoxy-indole-3-carbinol, 5-ethoxy-indole-3-carbinol, 5-propyloxy-indole-3-carbinol, 5-butyloxy-indole-3-carbinol, 5-amyloxy-indole-3-carbinol, N-methyl-indole-3-carbinol, N-ethyl-indole-3-carbinol, N-propyl-indole-3-carbinol, N-butyl-indole-3-carbinol, N-pentyl-indole-3-carbinol, 2-methyl-indole-3-carbinol, 2-ethyl-indole-3-carbinol, 2-propyl-indole-3-carbinol, 2-butyl-indole-3-carbinol and 2-pentyl-indole-3-carbinol.

The study of hepatotoxicity is presented in Exampe 1 of the specification as filed. In Example 1, I3C (indole-3-carbinol) or DIM (di-indolyl methane) were added to the diet of rats seven days prior to treatment with a hepatotoxic dose of ET-743. Then, a hepatotoxic dose of ET-743 was given, and hepatic changes were studied by assessment of alterations in plasma levels of bilirubin and the liver enzymes ALP and aspartate aminotransferase and by conventional histopathological investigation of liver tissue. The results of pre-administration of I3C and DIM are presented in Example 1.

With respect to enablement, the specification provides a detailed example in Example 1 for evaluating hepatotoxicity. In addition, researchers in the art of oncology and drug development are experienced in evaluating hepatotoxicity. Therefore, it would not represent undue experimentation to replace I3C or DIM in the experimental procedure provided in

Example 1 with any of the indole-3-carbinol derivative compounds listed in claim 9, and perform the subsequent steps as outlined in Example 1 as an example for evaluating hepatotoxicity.

Applicants respectfully request withdrawal of the rejection.

Claims 1-13 and 18-19 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement for the entire scope of the claims. The Office Action argues that while the claims are enabled for treatment of certain specific tumors with ET-743, the claims lack enablement for "the treatment of the vast variety of (cancerous and noncancerous) tumors within the scope of the claims" (Office Action, page 8). Applicants respectfully traverse.

Applicants note that ET-743 has been described in the scientific literature as having "demonstrated activity" against a "broad class of solid tumor cell lines," (see Van Kesteren, "Yondelis® (tracetedin, ET-743): the development of an anticancer agent of marine origin," Anti-Cancer Drugs, vol. 14, no. 7, August 2003, page 491, right column, last line; reference submitted in the IDS filed March 21, 2008). Activity against a "broad spectrum of tumors" including breast, non-small cell lung, ovary, melanoma, sarcoma, and renal tumors is described (see Van Kesteren, page 492, left column, lines 8-12).

The study of antitumor activity is presented in Example 2 of the specification as filed. In Example 2, tumor fragments were implanted subcutaneously into the flanks of rats. The growth of the tumors was measured with calipers according to conventional methods as described in the specification. The results of I3C and ET-743 on tumor growth are presented in Example 2.

With respect to enablement, the specification provides a detailed example in Example 2 for evaluating antitumor activity with ET-743. In addition, researchers in the art of oncology and drug develoment are experienced in evaluating tumor growth, for example with calipers to

measure the length and width of a tumor, or as described in Example 2. Therefore, while some experimentation may be required in order to implant a tumor in a rat, feed the rat ET-743, and then measure the tumor with calipers as described in Example 2, such experimentation is within the skill of the art, and it would not represent undue experimentation to implant a different tumor type compared to Example 2 in the specification.

Applicants respectfully request withdrawal of the rejection.

Claims 10-13 and 18-19 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement for the entire scope of the claims. The Office Action argues that while the claims are enabled for treatment of certain specific tumors with indole-3-carbinol, the claims lack enablement for "the treatment of the vast variety of tumors with a vast array of cruciferous indole compounds within the scope of the claims" (Office Action, page 10). Applicants respectfully traverse. However, in order to advance prosecution, the term "cruciferous indole compound" is replaced with the phrase "indole-3-carbinol or one or more derivatives or pharmaceutically acceptable salts thereof," wherein the indole-3-carbinol derivatives are selected from: 5-methyl-indole-3-carbinol, 5-ethyl-indole-3-carbinol, 5-propyl-indole-3-carbinol, 5-butyl-indole-3-carbinol, 5-pentyl-indole-3-carbinol, 5-methoxy-indole-3-carbinol, 5-ethoxy-indole-3-carbinol, 5-propyloxy-indole-3-carbinol, 5-butyloxy-indole-3-carbinol, 5-amyloxy-indole-3-carbinol, N-methyl-indole-3-carbinol, N-ethyl-indole-3-carbinol, N-propyl-indole-3-carbinol, N-butyl-indole-3-carbinol, N-pentyl-indole-3-carbinol, 2-methyl-indole-3-carbinol, 2-ethyl-indole-3-carbinol, 2-propyl-indole-3-carbinol, 2-butyl-indole-3-carbinol and 2-pentyl-indole-3-carbinol.

Applicants note that the claims are directed to combination therapy including ET-743, and ET-743 has been described in the scientific literature as having "demonstrated activity"

against a "broad class of solid tumor cell lines," (see Van Kesteren, "Yondelis® (tracetedin, ET-743): the development of an anticancer agent of marine origin," Anti-Cancer Drugs, vol. 14, no. 7, August 2003, page 491, right column, last line; reference submitted in the IDS filed March 21, 2008). Activity against a "broad spectrum of tumors" including breast, non-small cell lung, ovary, melanoma, sarcoma, and renal tumors is described (see Van Kesteren, page 492, left column, lines 8-12).

The study of antitumor activity is presented in Example 2 of the specification as filed. In Example 2, tumor fragments were implanted subcutaneously into the flanks of rats. The growth of the tumors was measured with calipers according to conventional methods as described in the specification. The results of I3C and ET-743 on tumor growth are presented in Example 2.

With respect to enablement, the specification provides a detailed example in Example 2 for evaluating antitumor activity with ET-743 and indole-3-carbinol. In addition, researchers in the art of oncology and drug develoment are experienced in evaluating tumor growth, for example with calipers to measure the length and width of a tumor. Example 2 provides evidence that the combination of ET-743 and indole-3-carbinol does not result in antagonism between the two agents. Therefore, while some experimentation may be required in order to implant a tumor in a rat, feed the rat an indole-3-carbinol derivate as specified instead of indole-3-carbinol, and then measure the tumor with calipers as described in Example 2, such experimentation is within the skill of the art, and it would not represent undue experimentation to implant a different tumor type or feed the rat a different derivative of indole-3-carbinol compared to Example 2 in the specification.

Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-13 and 18-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Donald *et al.* (Cancer Research, vol. 63, issue 18, pages 5902-5908, 2003) in view of Takahashi *et al.* (US 2004/0108086; corresponding to US 10/416,086). The Office Action argues that it would have been obvious to incorporate indole-3-carbinol and ET-743 in the same or separate medicaments in order to provide a convenient single administration, or to provide the flexibility of separate medicaments, or to "take advantage of the hepatoprotective properties of indole-3-carbinol against damage caused by ET-743" (Office Action, page 14). Applicants respectfully traverse on the basis that the Office Action's position with respect to obviousness is inconsistent with the Office Action's statements regarding enablement for the claims. In other words, a review of the Office Action's own statements clearly show that a prima facie case of obviousness has not been made.

It is a well-established principle of patent law that to make a prima facie case of obviousness, a reasonable expectation of success is required (See MPEP 2143.02 "Reasonable Expectation of Success Is Required"; see also *In re Merck & Co., Inc.*, 800 F.2d 1091). In addition, at least some degree of predictability is required (See MPEP 2143.02 "AT LEAST SOME DEGREE OF PREDICTABILITY IS REQUIRED").

However, based on statements from the Office Action itself, a prima facie case of obviousness has not been made. For instance, the Office Action states that "no one skilled in the art would accept the assertion that the instantly claimed composition could be predictably used to carry out the methods inferred by the claims and contemplated by the specification…a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success," (Office Action, page 12, lines 9-14). In addition, the Office Action states that "It is

unpredictable whether a drug can be used to treat a patient having a cancerous tumor," (Office Action, page 11, lines 3-4). The Office Action even states that "The unpredictable nature of cancer asssays has long been recognized," (Office Action, page 11, line 10). The Office Action also states that "it cannot be predicted if a drug will be successful in treating one type of cancer" (Office Action, page 8, lines 15-16). A similar statement with respect to hepatoprotection is also made (Office Action, page 6, line 17-19). The Office Action states that "no one skilled in the art would accept the assertion that the instantly claimed cruciferous indole compound could be predictably used reduce the hepatotoxicity of ET-743" (Office Action, page 7, lines 13-15).

As discussed above, Applicants traverse the rejection of the pending claims for lack of enablement. However, the fact remains that the official position of the Office Action is that the subject matter of the claims is "unpredictable" as stated on page 11, lines 3-4 and 10, and that no one skilled in the art would accept that the claimed compositions could be predictably used to carry out the methods of the specification, as stated on page 12, lines 9-14. Therefore, the Office Action has clearly failed to make a prima facie case of obviousness, which requires both a reasonable expectation of success and at least some degree of predictability. For the Office Action to maintain that the subject matter of the claims is simultaneously "unpredictable" while also having "at least some degree of predictability" would be a logical impossibility.

Applicants respectfully request withdrawal of the rejection as having failed to make a prima facie case of obviousness.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13566.105014. In the event that an extension of time is required, or which may be required in

addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105014.

Respectfully submitted,
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Dated: May 7, 2008

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